REMARKS

Claims 1-31 are pending in the application. Claims 1-14, 16-25, 27 and 28 are under consideration in the instant application. Claims 15, 26 and 29-31 have been withdrawn as being directed to non-elected subject matter in response to the Restriction Requirement mailed July 7, 2009. The elected claims were merely to comply with the Restriction Requirement and is not to be construed as surrender of any subject matter in the instant application. Applicants hereby reserve the right to pursue the subject matter of the withdrawn claims in one or more divisional patent applications.

Claims 2-8, 10, 12, 19 and 23 were amended to correct grammatical errors and to further define some of the subject matter as discussed below. Claim 20 was canceled without prejudice. Withdrawn claims 15, 26 and 30 were also amended to reflect the amendments in the pending claims. No new matter has been added by virtue of these amendments and entry is respectfully requested. Applicants hereby reserve the right herein, to pursue one or more canceled or amended subject matter in one or more continuation or divisional applications.

Specification

The first sentence of the disclosure was objected to for lacking clarity in claiming priority to the provisional application under 35 U.S.C. § 120. The appropriate amendments to the sentence have been made. No new matter has been added by virtue of this amendment and Applicants respectfully request withdrawal of the Examiner's objection.

Claim Objections

Claims 3, 10 and 19 were objected to by the Examiner for the following:

Claim 3 was objected to, for use of the acronym "SOCS". Applicants have amended claim 3 to provide the definition of "SOCS".

Claims 10 was objected to, for lacking the term "a" in line 1, after the phrase "the purification sequence is". Applicants have amended claim 10 to include the term "a".

Claim 19 was objected to, for grammatical errors in the phrase "staphylococcus enterotoxin B". Applicants have amended the claim to correct the grammatical errors and the phrase is now recited as "*Staphylococcus aureus*" enterotoxin B.

The Examiner has indicated that should claim 14 be found allowable, claim 20 would be objected to as being a substantial duplicate thereof. Applicants have canceled claim 20 without prejudice or disclaimer. Applicants herein reserve the right to pursue any amended or canceled subject matter in one or more divisional or continuation applications.

In view of the foregoing, Applicants respectfully request withdrawal of the Examiner's objections.

Claim Rejections Under 35 U.S.C. § 112

Claims 4, 5, 7, 8 and 12 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse.

The Examiner alleges that claim 4 does not further limit the independent claim since claim 4 "recites the nucleic acid sequence set forth in SEQ ID NO: 4" and claim 3 "requires" a "SOCS sequence and a membrane translocating sequence." In response, Applicants have amended claim 4 to recite that the sequence of the SOCS polypeptide is a human polypeptide and the membrane translocating sequence is set forth as SEQ ID NO: 2. Support is found throughout the application. See, for example, page 12, lines 1 to 26. No new matter has been added by virtue of these amendments and entry is respectfully requested.

Claim 5 was rejected "because it recites the nucleic acid sequence comprising the nucleotide sequence set forth in SEQ ID NO: 11" and claim 3 "requires" a "SOCS sequence and a membrane translocating sequence." In response, Applicants have amended claim 5 to recite that the nucleotide sequence of the human SOCS 3 polypeptide is set forth as SEQ ID NO: 11.

The Examiner has rejected claim 7 as being indefinite "as it is unclear whether open or closed term language is intended (i.e., "containing"). Applicants respectfully traverse. The MPEP §2111.03 states in pertinent part:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."). *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). In *Gillette Co. v. Energizer Holdings Inc.*, 405 F.3d 1367, 1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open-ended. "The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." *Id.* In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" that is by its nature closed. *Id.* The court also emphasized that reference to "first," "second," and "third" blades in the claim was not used to show a serial or numerical limitation but instead was used to distinguish or identify the various members of the group. *Id.*

Applicants submit that use of the term "containing" does not render the claim indefinite and respectfully request reconsideration and withdrawal of the rejection.

Claim 8 was rejected for reciting the term "composition" as it is dependent on claim 1 which recites a "polypeptide." In response, Applicants have amended claim 8 as per the Examiner's recommendation.

Claims 12, 13, 14, 16-22 were rejected as being indefinite. The Examiner alleges that claim 12 lacks clarity as to what the goal of claim 12 may be. Applicants respectfully disagree, however, in order to expedite and compact prosecution, Applicants have amended claim 12 to recite a method "preventing or treating an inflammatory disease in a subject." Support for the amendment is found throughout the specification. For example, page 37, paragraph 133; page 41, paragraph 144; page 43, paragraphs 154 and 156. The factors inciting inflammation disease are diverse ranging from exogenous and endogenous microbial agents, autoimmune injury to target organs (lupus, arthritis), or excessive accumulation of metabolic factors, such as uric acid in gouty arthritis. Frequently, the elimination of these inflammation-inducing factors is difficult (or impossible if their identity is unknown e.g. rheumatoid arthritis) yet they evoke inflammation as the common mechanism of majority of diseases. Thus, anti-inflammatory therapy is primary e.g. in lupus or rheumatoid arthritis or adjunctive e.g. in polymicrobial sepsis, to reduce uncontrolled inflammatory response that hampers clearance of infection. Thus, the treatment of inflammation using the SOCS compositions, as demonstrated in the Examples section of the specification, is applicable to diverse diseases mediated by inflammation. In addition, the specification provides many examples of what can cause inflammatory diseases or inflammation mediated diseases. See, for example, page 37, lines 30-34 through to page 38, lines 1-17 (general diseases and conditions that give rise to inflammation – claims 12, 13, 14, 16-22). Specific examples of causes of inflammation are also provided, see, for example, page 38, lines 24-29 (viral and bacterial infections - claims 16, 17, 18, 19); page 41, lines 19-21 (biological weapons – claim 22); page 42, lines 20-32 (biological systems); page 43, lines 14-20 (surgery- claim 21); page 43, lines 26-33 (transplantation). No new matter has been added by virtue of these amendments and entry is respectfully requested. Claim 12 fully complies with 35 U.S.C. § 112, second paragraph. Since claims 13, 14, and 16-22 depend on claim 12, these claims also comply with 35 U.S.C. § 112, second paragraph.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejections.

Claims 7, 12-14, 16-25 were rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse.

The Examiner alleges that the "specification, while being enabling for an isolated or cultured host cell comprising the vector of claim 6, does not reasonably provide enablement for a cell containing the vector of claim 6." As discussed above, the term "containing" can be used for the term "comprising." However, without acquiescing to the Examiner's positions and to compact and expedite prosecution, Applicants have amended claim 7 to recite the term "comprising." In addition, Applicants have amended claim 7 to include the recitation of the sequences corresponding to the SOCS and membrane translocating sequences which are encoded by the vector of claim 6.

The Examiner has also alleged, (page 5, paragraph 9 of the Office Action) that the specification "does not reasonably provide enablement for a method comprising administering a polypeptide comprising a SOCS sequence and a membrane translocating sequence." Applicants respectfully disagree. Applicants clearly show that the polypeptide is delivered to both the blood cells and other organ systems of an animal. See, for example, page 53, lines 33-34 through to page 54, lines 1-12. In addition, Applicants track the *in vivo* intracellular delivery of the compositions. See, for example, page 48, lines 21-3 through to page 49, lines 1-4. Applicants also teach the treatment of inflammation *in vivo* by administering the compositions to the animals. See, for example, page 49, lines 5-34 through to page 50, lines 1-5. In addition, Applicants teach that three SOCS sequences (SOCS1, SOCS3, and truncated SOCS3 with extended half-life) can be used and provide one of ordinary skill in the art the pertinent disclosure to make and use any SOCS sequence. For example, the specification provides sequences for various SOCS molecules or accession numbers to obtain these sequences (see, for example, page 12, lines 24-31). The disclosure further identifies the functional characteristics of the SOCS sequences (see, for example, page 11, lines 16-33, through to page 12, lines 1-15). See, also, for example, page 12, lines 16 – 31. Working examples are also provided, which teach one of ordinary skill in the art to: isolate, purify and express SOCS sequences. These can then be tested as to whether they are, for example, anti-inflammatory as discussed above. Thus, Applicants teach that the compositions comprise a SOCS sequence (e.g. SOCS-1, SOCS-3, truncated SOCS3, including other mutants) and a membrane

translocating sequence (MTS); that these compositions are administered to subjects; that the compositions are delivered *in vivo*; that these compositions are delivered intracellularly; that these compositions function to decrease inflammation as measured by many parameters Applicants submit that the specification and claims more than meet any enablement requirements. Applicants provide Crocker *et al* (Exhibit A) which summarizes SOCS biology [1].

The Examiner also alleges on page 7, last paragraph of the Office Action that "the specification does not teach any methods or working examples that indicate a nucleic acid encoding a SOCS sequence and a membrane translocating sequence is introduced and expressed in a cell for therapeutic purposes." Applicants respectfully disagree. Applicants teach the construction of a vector expressing a SOCS polypeptide and a membrane translocating sequence and then production, purification, and intracellular delivery of SOCS 1 and SOCS3 recombinant proteins in cell-penetrating form. See, for example, page 51, lines 20-33 through to page 52, lines 1-12. Applicants further teach that the polypeptides expressed from these vectors in producer cells (bacterial or mammalian) and stringently purified are delivered intracellularly; that these molecules are functional *ex vivo* in primary bone marrow- derived macrophages or transformed cell lines, as measured by phosphorylation of STAT1 and cytokine measurements, and *in vivo* as measured by increased survival of the subject due to attenuation of massive liver inflammation and apoptosis; that there is detection of the delivered proteins in both in the inflammation-relevant blood cells and in organs. See, for example, page 52, lines 19-33; page 53, lines 1-33 through to page 54, lines 1-12. As Examiner stated, the gene transfer approach practiced by those skilled in the art did not overcome inherent difficulties in facile and controlled delivery of gene or other genes that encode intracellular proteins. However, in contrast to the Examiner's assertions that Applicants' claims are directed to gene therapy, Applicants instead teach that teach the replacement of depleted stores of intracellular physiologic anti-inflammatory protein, such as SOCS3, with recombinant, cell-penetrating forms of SOCS which was found to be a feasible alternative to gene transfer of SOCS3. The essence of Applicants intracellular protein therapy approach was based on the data in the specification whereby the intracellular delivery of the SOCS molecules are recombinant proteins in cell-penetrating form. In the specification, supported by Applicant Hawiger's subsequently

[1] B. Crocker *et al. Seminars in Cell & Developmental Biology* 19 (2008) 414–422

published peer-reviewed papers [2]the applicants provide examples of experimental protocols that validate the utility of their invention. Thus, in contrast to the Examiner's allegations, the disclosure is not "merely an invitation to the artisan to use the current invention as a starting point for further experimentation." As discussed above, Applicants teach the intracellular delivery of the recombinant proteins in cell-penetrating form for which Applicant's specification more than meets the requirements of 35 U.S.C. § 112, first paragraph.

The MPEP § 2164.02 states in pertinent part:

> An applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

Applicants submit that the specification and the claims that are directed to the invention more than meet the enablement requirements. In addition to the above, without acquiescing to the Examiner's positions, Applicants have also amended the claims. These amendments are solely for responding to this Office Action and are not to be construed as surrender of any subject matter. Applicants reserve the rights herein, to pursue any canceled or amended subject matter in one or more continuation or divisional applications.

The Examiner also alleges on page 9, first paragraph of the Office Action, that there is no teaching regarding the roles of different SOCS molecules and that it would require undue experimentation to "determine the role of SOCS-2, SOCS-4, SOCS-5, SOCS-6, and SOCS-7 in inflammation." See, page 10, paragraph continuing from page 9 of the Office action. Applicants respectfully disagree. The specification provides sequences for SOCS molecules (see, for example, page 12, lines 24-31). Working examples are also provided as to how to express SOCS sequences in bacterial or mammalian cells to produce recombinant proteins in cell-penetrating form for

[2] See, for example, Jo *et al* 2005 *Nature Med.*, 2005 Aug;11(8):892-8; DiGiandomenico *et al.* 2009 *Science Signaling*; 2009 Jul 21;2(80):ra37; and Fletcher *et al* 2010 Apr 19. *J. Biol. Chem* [Epub ahead of print]

intracellular delivery *ex vivo* and *in vivo*. These can then be tested as to whether they are, for example, anti-inflammatory as discussed above. Thus, one of ordinary skill in the art would have the necessary teachings available by the instant disclosure.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejections.

Claim Rejections Under 35 U.S.C. § 102

Claim 4 was rejected under 35 U.S.C. § 102(b) as being anticipated by Hilton *et al.* (U.S. Patent 6,323,317).

Applicants respectfully traverse. However, to compact and expedite prosecution, Applicants have amended claim 4 to include the membrane translocating sequence. As such, Hilton *et al.*, do not anticipate each and every claim limitation of claim 4.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1, 3, 4, 6-12, 23, 27 and 28 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hilton *et al.* (US Patent 6,323,317) in view of Lin *et al.* (WO 99/49879).

Applicants respectfully traverse.

As the Examiner acknowledges, Hilton *et al.* do not teach a polypeptide comprising a SOCS sequence and a membrane translocating sequence. In addition the Examiner acknowledges that Hilton *et al.* also do not teach a nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocating sequence.

The Examiner alleges on page 12, second full paragraph of the Office Action, that Lin *et al.* teach a membrane translocating sequence (MTS) for importing protein molecules into a cell and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence. The Examiner further alleges that it would have been obvious to one of ordinary skill in the art to modify Hilton *et al* by fusing these molecules to the MTS of Lin *et al*. Applicants respectfully disagree. The combination of SOCS and an MTS would not have been obvious to one of skill in the art. The engineering of a fusion protein that combines SOCS protein and membrane translocating sequence is not immediately obvious for several reasons. Until the filing of the instant application and the inventors published their seminal study in 2005 (Jo *et al Nat. Med*) on proving their concept of intracellular protein therapy with cell-penetrating form of SOCS3 protein for *ex vivo* and *in vivo* intracellular delivery would not have been obvious to one of skill in the art. Hilton *et al* and Lin *et al* did not teach, suggest, or provide the motivation for engineering a protein that was able to cross cell membrane and suppress inflammation. Hilton *et al* did not provide any teachings that would lead one of ordinary skill in the art to produce a SOCS protein to cross cell membrane *ex vivo* and *in vivo*. Taking Hilton *et al* in view of Lin *et al*, did not provide the teachings that would allow one of ordinary skill in the art that MTS can be specifically used to engineer cell-penetrating SOCS3 for treatment of inflammation-mediated diseases. Nor did they propose to test the hypothesis that replacement of depleted stores of intracellular physiologic protein, such as SOCS3, a feasible alternative to gene transfer of SOCS3. Again, as Examiner aptly stated, gene transfer approach practiced by those skilled in the art did not overcome inherent difficulties in facile and controlled delivery of SOCS3 gene. In contrast, the inventors proposed in their US PHS National Institute of Health grant application HL-69452, submitted to granting agency in April 2001, the concept of intracellular delivery of cell-penetrating forms of SOCS1 and SOCS3 as a facile and versatile alternative to gene therapy. A fusion protein, as suggested by the Examiner would have required proof of concept difficult to obtain without meticulous selection of bacterial or mammalian expression system for production of such a fusion protein. Therefore, the combination of SOCS3 (or SOCS1) with MTS may have precluded its expression or if expressed might rendered the protein insoluble. Such an outcome would have resulted in a protein that could not and would

not be delivered intracellularly thereby defeating the purpose of the combined molecular entities. This in and of itself, would teach away from one of skill in the art to combine the two teachings.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 12, 13, 14, 20, 23, 24 and 25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Shouda *et al.* (*J. Clin. Invest* 108(12): 1781-1788, 2001) in view of Hilton *et al.* (US Patent 6,323,317) and Lin *et al.* (WO 99/49879).

Applicants respectfully traverse.

The Examiner alleges that the injection of an adenovirus vector carrying a SOCS3 cDNA renders Applicants' invention obvious in view of Hilton *et al* and Lin *et al.* Applicants respectfully disagree with the Examiner's allegations. The Examiner acknowledges that Shouda *et al.* do not teach a recombinant protein comprising a SOCS sequence and a membrane translocating sequence. As discussed above, it would not be obvious to one of ordinary skill in the art to combine SOCS and MTS including the Shouda *et al* study. Thus, neither Hilton *et al.* in view of Lin *et al.* provide the necessary motivation to combine the SOCS and MTS as taught by Applicants. Furthermore, Shouda *et al.*, do not even contemplate therapy by means of intracellular delivery of the SOCS3 protein into a cell for the treatment of rheumatoid arthritis. Shouda *et al.*, only contemplate treating the localized symptoms of rheumatoid arthritis by attempting to locally inject their vector. The most of the vector containing gene of interest i.e.SOCS3 remains in the fluid phase and is broken down. This is in stark contrast to Applicants invention which is directed *inter alia,* to the importation of the therapeutic SOCS proteins into cells and can be systemically disseminated throughout various cells, tissues, organs and fluids rendering a superior therapy. The Applicants invite the Examiner to consult a series of original reports published by them in peer-reviewed journals (Jo *et al* 2005 *Nature Med.*; DiGiandomenico *et al* 2009 *Science Signaling*; and Fletcher *et*

al 2010 *J. Biol. Chem.*), which support the originality of their invention and meticulously document that their invention requires specifically defined condition for production, purification, and administration of cell-penetrating forms of SOCS1, SOCS3, and its long-acting truncation mutant.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

Applicants invite the Examiner to call the undersigned if it is believed that the above restriction election is incomplete or improper in any way, or if a telephonic interview will expedite the prosecution of the application to an allowance.

The Commissioner for Patents and Trademarks is hereby authorized to charge any deficiency or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 14-1437.

Dated: June 3, 2010

Respectfully submitted,

By /Nicholas A. Zachariades /
Nicholas A. Zachariades
Registration No.: 56,712
NOVAK DRUCE+ QUIGG, LLP
CityPlace Tower
525 Okeechobee Blvd., 15th Floor
West Palm Beach, FL 33401
Phone: 561-847-7890
Fax: 561-847-7801
e-mail: nicholas.zachariades@novakdruce.com